was filed, had possession of the claimed invention. The Examiner alleges that the instant disclosure fails to provide adequate written description of: the co-administration of 2-methoxyadenosine with any other substance known to act as an analgesic; the "prevention" of pain associated with any disease condition by the administration of 2-methoxyadenosine; and the effective treatment of pain associated with any neurodegeneration including Alzheimer's disease, HIV, AIDS, ARC, silicosis, myasthenia gravis, Crohn's disease, bacterial meningitis, and nearly all of the other diseases listed generically or specifically in any of claims 11, 15, and 18.

According to M.P.E.P. § 2163.04, a description as filed is presumed to be adequate, unless or until sufficient evidence or reasoning to the contrary has been presented by the examiner to rebut the presumption. See, e.g., In re Marzocchi, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). The examiner, therefore, must have a reasonable basis to challenge the adequacy of the written description. The examiner has the initial burden of presenting by a preponderance of evidence why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims. Wertheim, 541 F.2d at 263, 191 USPQ at 97. A general allegation of "unpredictability in the art" is not a sufficient reason to support a rejection for lack of adequate written description.

According to M.P.E.P. §2163 II.A.3.(a), written description sufficient to establish Applicant's possession of the claimed invention can include, for example, description of an actual reduction to practice of the claimed invention. Alternatively, an applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. Enzo Biochem, 323 F.3d at 964, 63 USPQ2d at 1613.

Written Description Rejection under 35 U.S.C. § 112, 1st Paragraph re "Co-administration"

The written description rejection under 35 U.S.C. § 112, 1st paragraph re "co-administration" is improper because no evidence has been presented to rebut the application's presumption of adequate written description, nor does the Examiner state why a person skilled in the art would not recognize in applicant's disclosure a description of the claimed invention.

Moreover, contrary to the Examiner's allegation that the instant disclosure fails to provide adequate written description of the co-administration of 2-methoxyadenosine with any other analgesic agent, the specification includes an actual reduction to practice of the claimed method "wherein another analgesic agent is administered to the subject" (claim 27). For instance, in Example 5, spongosine (2-methoxyadenosine) was co-administered with gabapentin, a known analgesic agent for treating neuropathic pain (specification, page 9, lines 1-12). Spongosine (2-methoxyadenosine) and gabapentin together inhibited static allodynia in an *in vivo* model for neuropathic pain. FIG. 5 shows that the observed co-administration effects, indicated by (■), are similar to the predicted anti-hyperalgesic effect (derived from the dose response curves obtained with each agent alone) if the effects of the two compounds are additive (●). Further, the specification describes additional aspects of co-administration, including considerations for dosing and for selecting other analgesic agents for combined effects (specification, page 6, line 7-page 7, line 6).

For at least these reasons, the rejection is overcome. Applicant respectfully requests that the Examiner withdraw the corresponding rejection.

Written Description Rejection under 35 U.S.C. § 112, 1st Paragraph re "Prevention"

The written description rejection under 35 U.S.C. § 112, 1st paragraph re "prevention" is improper because no evidence has been presented to rebut the application's presumption of adequate written description, nor does the Examiner state why a person skilled in the art would not recognize in applicant's disclosure a description of the claimed invention.

Moreover, contrary to the Examiner's allegation of insufficient written description regarding the "prevention" of pain, the specification provides more than adequate written

description because it recites multiple actual reductions to practice of the claimed method using *in vivo* pain models.

In the medical arts, a "preventive" method is one "[a]cting to ward off or hinder the occurrence of something such as a disease," (Exhibit A, Melloni's Illustrated Medical Dictionary, 4th Ed., Melloni, JB & Dox, I, eds, Parthenon, New York, 2002 p. 528), "tending to slow, stop, or interrupt the course of an illness or to decrease the incidence of a disease," (Exhibit B, Mosby's Medical, Nursing and Allied Health Dictionary, 4th Ed., Anderson et al., Mosby, St. Louis, MO, 1994, p. 1272), or "[h]indering the occurrence of something, esp. disease. SYN: prophylactic" (Exhibit C, Cyclopedic Medical Dictionary, 16th Ed., Taber, CW & Thomas, CL, eds, F.A. Davis, Philadelphia, 1989, p. 1483). Consequently, one of ordinary skill in the art will understand that the claimed "method of preventing . . . pain which comprises administering spongosine (2-methoxyadenosine) to a subject in need of such prevention," includes a prophylactic treatment that can ward off, hinder, slow, stop, decrease, or interrupt the course, incidence, or occurrence of pain, as is exemplified in the specification.

For instance, Example 1 provides experimental data showing that in a rat model for inflammatory pain, spongosine (2-methoxyadenosine) prevents pain with efficacy comparable to indomethacin, a known anti-inflammatory analgesic (specification, page 7, line 23- page 8, line 2). Example 1 employs a carrageenan induced thermal hyperalgesia (CITH) model in the rat. Carrageenan (2%, 10 microlitres) was administered into the rat and a heat source was placed close to the treated and untreated hind paws. FIG 1A shows that the difference in paw withdrawal latency compared to vehicle is reduced with spongosine (2-methoxyadenosine), and that reduction is comparable to that achieved with indomethacin.

Further, Example 2 provides experimental data showing that in a rat model for neuropathic pain, spongosine (2-methoxyadenosine) administration was just as or more effective in preventing pain than carbamazepine, a known analgesic for neuropathic pain (specification, page 8, lines 3-11). Thermal hyperalgesia was caused by chronic constriction injury of the rat sciatic nerve. FIG. 2 shows that administration of spongosine (2-methoxyadenosine) reduced the hyperalgesia as shown by the reduction in the difference between the withdrawal latencies, and

spongosine (2-methoxyadenosine) was as, or more, effective than carbamazepine. Moreover, as noted above, Example 5 shows that administration of spongosine (2-methoxyadenosine) displayed an additive analgesic effect when co-administered with gabapentin in a rat model for neuropathic pain.

Consequently, the specification reasonably conveys to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of "[a] method of preventing . . . pain which comprises administering spongosine (2-methoxyadenosine) to a subject in need of such prevention . . ." as claimed. Applicant respectfully requests that the Examiner withdraw the corresponding rejection.

Written Description Rejection under 35 U.S.C. § 112, 1st Paragraph re Diseases

The Examiner's alleges that there is insufficient written description regarding the "effective treatment of pain associated with any cancer including pancreatic cancer or brain cancer, any auto-immune disease, epilepsy, neurodegeneration including Alzheimer's disease, HIV, AIDS, ARC, silicosis, myasthenia gravis, Crohn's disease, bacterial meningitis, and nearly all of the other diseases listed generically or specifically in any of claims 11, 15, and 18."

As a preliminary matter, Applicant notes that the rejection at page 3 identifies specific diseases which were not disclosed in the present application, e.g., ". . . brain cancer . . . epilepsy, . . . Alzheimer's disease."

As it relates to diseases cited in the application, this written description rejection under 35 U.S.C. § 112, 1st paragraph re "effective treatment of pain associated with" the recited conditions is improper because no evidence has been presented to rebut the application's presumption of adequate written description, nor does the office action state why a person skilled in the art would not recognize in applicant's disclosure a description of the claimed invention.

Moreover, contrary to the Examiner's allegation of insufficient written description re "effective treatment of pain associated with" the recited conditions, the specification provides more than adequate written description because it recites multiple actual reductions to practice

using *in vivo* models of inflammatory and neuropathic pain, further coupled with diseases and conditions known to be correlated with inflammatory and neuropathic pain.

For example, as described elsewhere herein, the specification includes multiple actual reductions to practice wherein the claimed method is shown to be effective with *in vivo* pain models that have inflammatory or neuropathic characteristics, e.g., Examples 1, 2, 4, and 5. Moreover, each of the diseases and conditions recited in the specification and claims exhibits neuropathic and/or inflammatory pain as described in the specification, for example at page 4, line 4-page 5, line 7. For example, referring to diseases common to the application and the Examiner's rejection, diseases that can involve neuropathic pain include HIV and cancer (page 4, line 6), and diseases that can involve inflammatory pain include cancer, HIV, AIDS related complex, silicosis, myasthenia gravis, Crohn's disease, bacterial meningitis (page 4, line 29, page 5, lines 2-5).

For at least these reasons, the specification reasonably conveys to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed methods. Applicant respectfully requests that the Examiner withdraw the corresponding rejection.

Enablement Rejection under 35 U.S.C. § 112, 1st Paragraph

Claims 11-31 stand rejected under 35 U.S.C. § 112, first paragraph, because while the Examiner concedes that the specification enables the treatment of inflammation and hypertension, the Examiner alleges that the specification does not reasonably provide enablement for the treatment of any other disease condition.

As a preliminary matter, Applicant notes that the present claims are directed to methods of treatment or prevention of pain.

The claimed invention is enabled when any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). The factors which may be considered when determining whether a disclosure is enabling and whether any necessary experimentation is "undue" include, for

example, (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. *Id.* Further, a patent need not teach, and preferably omits, what is well known in the art. See, *e.g., In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991).

(A) The breadth of the claims;

The Examiner alleges that the claims are excessively broad in scope because the Examiner asserts that the claims are directed to the treatment of pain associated with the recited diseases, and the Examiner alleges that the disclosure fails to define how to effectively treat the majority of these diseases.

Contrary to the Examiner's allegation, the claims are not excessively broad because the application supports the breadth of the invention as claimed. Claim 11 recites "[a] method of preventing, treating, or ameliorating pain which comprises administering spongosine (2-methoxyadenosine) to a subject in need of such prevention, treatment, or amelioration." As noted elsewhere herein, the specification recites multiple working examples which demonstrate that the claimed method is effective on *in vivo* models of inflammatory and neuropathic pain. Moreover, the specification and claims recite specific diseases and conditions known to be correlated with inflammatory and neuropathic pain, for example as described at page 4, line 4-page 5, line 7 and recited in the claims. The Examiner provides no evidence or reasoning to show why the entire scope of claim 11 would not be enabled, let alone the specific recited diseases and conditions known to be correlated with inflammatory and neuropathic pain.

(B) The nature of the invention;

The nature of the invention is "[a] method of preventing, treating, or ameliorating pain which comprises administering spongosine (2-methoxyadenosine) to a subject in need of such prevention, treatment, or amelioration."

(C) The state of the prior art;

The prior art is concerned with the treatment of pain by administering analgesics. As the Examiner acknowledges, the prior art does not identify the analgesic efficacy of spongosine (2-methoxyadenosine) as employed in the claimed method.

(D) The level of one of ordinary skill;

The level of skill in the art of pain management is extremely high. One of ordinary skill includes, for example, a physician experienced in preventing, treating, or ameliorating pain by administering an analgesic to a subject in need of such prevention, treatment, or amelioration. Such physicians are experienced in selecting among available analgesics and determining an effective dose. For example, according to the American Board of Pain Medicine's "Definition of Pain Medicine:"

> The specialty of Pain Medicine is concerned with the prevention, evaluation, diagnosis, treatment, and rehabilitation of painful disorders. Such disorders may have pain and associated symptoms arising from a discrete cause, such as postoperative pain or pain associated with a malignancy, or may be syndromes in which pain constitutes the primary problem, such as neuropathic pains or headaches. The diagnosis of painful syndromes relies on interpretation of historical data; review of previous laboratory, imaging, and electrodiagnostic studies; behavioral, social, occupational and avocational assessment; interview and examination by the pain specialist; and may require specialized diagnostic procedures, including central and peripheral neural blockade or monitored drug infusions. The special needs of the pediatric and geriatric populations are considered when formulating a comprehensive treatment plan for these patients.
>
> The pain physician serves as a consultant to other physicians but is often the principal treating physician and may provide care at various levels, such as direct treatment, prescribing medication, prescribing rehabilitative services, performing pain relieving procedures, counseling of patients and families, direction of a multidisciplinary team, coordination of care with other healthcare providers and consultative services to public and private agencies pursuant to optimal healthcare delivery to the patient suffering from a painful disorder. (Exhibit D, http://www.abpm.org/what/index.html, accessed October 28, 2007)

The American Academy of Pain Medicine provides a similar "Definition of Pain Medicine." See Exhibit E, http://www.painmed.org/about/, accessed October 28, 2007.

The Examiner alleges that one of ordinary skill in the art is expected to be familiar with the details of the medicinal treatment of the diseases recited in the claims and further alleges that such familiarity is a literal impossibility because neither one nor a dozen practitioners could meet such a requirement.

Firstly, contrary to the Examiner's allegation, there is no requirement found in the M.P.E.P. or in the case law that the entire breadth of a claim must be able to be practiced by any single person or particular group of persons.

Secondly, the Examiner's allegation is contrary to the established practice of pain management. For example, according to the American Board of Pain Medicine, "[t]he pain physician . . . is competent to treat the **entire range** of painful disorders encountered in delivery of quality health care." (emphasis added, Exhibit D). The American Academy of Pain Medicine concurs, stating "[t]he pain physician . . . is competent to treat the entire range of pain encountered in the delivery of quality health care." (Exhibit E). Therefore, contrary to the Examiner's allegation, a physician may specialize in preventing, treating, or ameliorating pain without being an expert in every disease or condition which may conceivably cause pain.

(E) The level of predictability in the art;

The Examiner alleges that the predictability in the art is low because the Examiner asserts that the disclosure lacks guidance directed to treatment of the cited diseases and conditions.

Contrary to the Examiner's allegation, the level of predictability in the art is high because the numerous examples demonstrate the effectiveness of the claimed method against several major pain mechanisms known in the art to be involved in a wide range of pain-causing diseases or conditions. Furthermore, the level of predictability in the art is high because one of ordinary skill in the art of pain management is experienced in treating a subject in pain regardless of whether the particular disease or condition that causes the pain is known. See the definitions of

pain medicine provided by the American Board of Pain Medicine and American Academy of Pain Medicine as reproduced in Exhibits D and E.

(F) The amount of direction provided by the inventor;

The Examiner alleges that the disclosure only supplies two and one-half pages of guidance and an indication of how to treat pain associated with only a few model test hosts wherein the pain has been induced 'artificially.'

Contrary to the Examiner's allegation, Applicant has provided substantial direction. As noted above, one of ordinary skill in the art is experienced in selecting among available analgesics and determining an effective dose. The specification provides five working *in vivo* examples which demonstrate effective usage of the claimed method, for example, against inflammatory-related pain (Example 1) and neuropathic pain (Examples 2, 4, and 5); as lacking side effects at a dosage that is effective against pain (Example 3); and as being effective through a mechanism that can complement other analgesics (Examples 4 and 5), including demonstrating effective co-administration (Example 5). Further, the specification gives substantial guidance regarding pharmaceutical compositions (page 5, lines 10-11), dosage ranges, including guidance for dosing to avoid side effects (page 5, line 12 to page 6, line 3), routes of administration (page 6, lines 4-5), frequency of administration (page 6, line 6), and guidance regarding co-administration with other analgesics, for example to reduce side effects (page 6, line 7 to page 8, line 6). Consequently, the specification provides substantial direction which permits one of ordinary skill in the art to use the claimed method.

Further, the Examiner's assertion that the pain has been caused artificially is inapposite. The Examples describe the efficacy of the claimed method in working examples against known, *in vivo* models of pain, for example, neuropathic pain and inflammatory pain, and the specification and claims recite specific diseases and conditions known to be correlated with neuropathic pain and/or inflammatory pain. The Examiner provides no reasoning or evidence to doubt the correlation between the working *in vivo* examples and the claimed method, including the specifically recited diseases and conditions.

(G) The existence of working examples; and

As noted above, the specification provides five working *in vivo* examples which demonstrate the effectiveness of the claimed method.

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The Examiner alleges that the quantity of experimentation needed to make or use the invention is deemed to be excessive because the Examiner asserts that the specification is entirely inadequate to provide the guidance necessary to practice the claimed method predictably in the vast majority of the recited disease conditions.

Contrary to the Examiner's allegation, the quantity of experimentation needed to use the invention is well within the experimentation routinely practiced by one of ordinary skill in the art. As noted above, the level of skill in the art is high and one of ordinary skill in the art is experienced in selecting among available analgesics and determining an effective dose, and consequently one of ordinary skill in the art routinely experiments to determine dosage and analgesic for a subject in pain. In particular, the American Board of Pain Medicine's "Definition of Pain Medicine" reveals that the art relies on a substantial amount of experimentation in that, for example, "[t]he diagnosis of painful syndromes relies on interpretation of historical data; review of previous laboratory, imaging, and electrodiagnostic studies; behavioral, social, occupational and avocational assessment; interview and examination by the pain specialist; and may require specialized diagnostic procedures, including central and peripheral neural blockade or monitored drug infusions." (Exhibit D; see also the American Academy of Pain Medicine's definition in Exhibit E). Consequently, it is routine for one of ordinary skill in the art to conduct a substantial amount of experimentation.

Therefore, the full scope of the claimed invention is enabled because the breadth of the claims is consistent with the support in the specification, the prior art does not identify the analgesic efficacy of spongosine (2-methoxyadenosine) as employed in the claimed method, the

level of skill in the art of pain management is high, the level of predictability in the art is high, Applicant has provided substantial direction, the specification provides five working *in vivo* examples, the quantity of experimentation needed to use the invention is well within the experimentation routinely practiced by one of ordinary skill in the art. For at least the preceding reasons, a prima facie case of lack of enablement has not been made. Applicant respectfully requests that the Examiner withdraw the corresponding rejection.

Objections Regarding Claims 14, 15 and 18

The Examiner helpfully notes apparent informalities in the terms and phrases "pelvicpain" in claim 15, "colitis and pyresis" in claim 18, and "or adverse effects" in claim 18.

Applicant has amended the claims to address the preceding informalities. Applicant respectfully requests that the Examiner withdraw the corresponding objection.

Indefiniteness Rejection under 35 U.S.C. § 112, 2nd Paragraph

Claims 14, 18 and 27 stand rejected under 35 U.S.C. § 112, second paragraph as being indefinite.

The Examiner alleges that the term "disease that causes damage to sensory neurons" in claim 14 is incomplete because the particular diseases implied by this phrase have not been defined in the claim. Likewise, the Examiner alleges that the term "arthritic conditions" in claim 18 has not been further defined in the claim.

The rejection of claims 14 and 18 is improper because during examination, the claims must be interpreted as broadly as their terms reasonably allow. *In re American Academy of Science Tech Center*, 367 F.3d 1359, 1369, 70 USPQ2d 1827, 1834 (Fed. Cir. 2004). Further, the terms of the claim must be given their plain meaning unless the plain meaning is inconsistent with the specification. *In re Zletz*, 893 F.2d 319, 321, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989). Moreover, "a particular embodiment appearing in the written description may not be read into a claim when the claim language is broader than the embodiment." Superguide Corp. v. DirecTV Enterprises, Inc., 358 F.3d 870, 875, 69 USPQ2d 1865, 1868 (Fed. Cir. 2004). Applicant

respectfully submits that the plain meaning of the generic term "disease that causes damage to sensory neurons" is clear to one of ordinary skill in the art. By alleging that the generic term "disease that causes damage to sensory neurons" is incomplete without recitation of specific diseases, the Examiner fails to interpret the claims as broadly as the plain meaning of the term allows. Further, requiring Applicant to recite specific diseases in the claims amounts to impermissibly requiring Applicant to import limitations into the claims from the specification. Likewise, the plain meaning of the generic term "arthritic conditions" in claim 18 is clear to one of ordinary skill in the art and need not be further defined in the claim.

For at least these reasons, claims 14 and 18 are not indefinite. Applicant respectfully requests that the Examiner withdraw the corresponding rejections.

The Examiner alleges that the term "further comprising" or the like is needed to provide a proper basis for expansion of the scope of the subject matter of claim 11, and consequently that claim 27 lacks antecedent basis in claim 11.

Claim 11 recites "A method of preventing, treating, or ameliorating pain which comprises administering spongosine (2-methoxyadenosine) to a subject in need of such prevention, treatment, or amelioration." Claim 27, as amended, recites "[t]he method of claim 11, wherein an analgesic agent is co-administered to the subject." By introducing the new term "analgesic agent" with the term "an," claim 27 maintains proper antecedent basis with claim 11 and does not require recitation of a term such as "further comprising." Furthermore, a term such as "further comprising" may imply that an active step of co-administering an analgesic agent is required. By reciting "an analgesic agent is co-administered to the subject," Claim 27 permits, for example, a subject to which "an analgesic agent" has already been administered, as well as permitting an active step of co-administering "an analgesic agent" to the subject.

For at least these reasons, claim 27 is not indefinite. Applicant respectfully requests that the Examiner withdraw the corresponding rejection.

Obviousness-type double patenting rejections

Claims 11-31 stand provisionally rejected under the judicially created doctrine of obviousness type double patenting over claims 16-33 of co-pending Application Ser. No. 10/547,455, filed March 5, 2004, and claims 13-24 of co-pending Application Ser. No. 10/547,454, filed March 5, 2004.

The allegedly conflicting claims of Application Ser. Nos. 10/547,455 and 10/547,454, have not been patented. For this reason, the present rejection is a provisional obviousness-type double patenting rejection. In view of the amendments and remarks presented herein, it is Applicant's understanding that the provisional obviousness-type double patenting rejection is the only rejection remaining in the present application. Accordingly, the double patenting rejection should be withdrawn to permit the present application to issue as a patent. Further, with respect to provisional obviousness type double patenting rejections over co-pending applications, M.P.E.P. § 804.I.B.1 provides

> If a "provisional" nonstatutory obviousness-type double patenting (ODP) rejection is the only rejection remaining in the earlier filed of the two pending applications, while the later-filed application is rejectable on other grounds, the examiner should withdraw that rejection and permit the earlier-filed application to issue as a patent without a terminal disclaimer.

The present application, filed December 9, 2003, is the earlier filed application because co-pending Application Ser. Nos. 10/547,455 and 10/547,454 were filed March 5, 2004. In view of the amendments and remarks presented herein, it is Applicant's understanding that the provisional obviousness-type double patenting rejection is the only rejection remaining in the present application. Moreover, no terminal disclaimer is required for the present application because neither of co-pending Application Ser. Nos. 10/547,455 and 10/547,454 has issued as a patent but are presently rejected on grounds other than provisional nonstatutory double patenting. Therefore, Applicant respectfully requests that the Examiner withdraw the corresponding rejection and permit the present application to issue as a patent without a terminal disclaimer. Applicants respectfully request that the Examiner withdraw the rejection.

Regarding the Examiner's requirement under 37 C.F.R. § 1.78(b) that either the conflicting claims be canceled from all but one application or that a clear line of demarcation be

maintained between the applications, Applicant notes that under M.P.E.P. § 804.I.B.1, as argued above, the Examiner should withdraw the corresponding rejection and permit the present application to issue as a patent without a terminal disclaimer. Further, the present claims, drawn in part to spongosine (2-methoxyadenosine), are separate from claims 16-33 of co-pending Application Ser. No. 10/547,455, which exclude spongosine (2-methoxyadenosine) by proviso. Furthermore, the present claims, drawn in part to methods of treating or preventing pain, are separate from claims 13-24 of co-pending Application Ser. No. 10/547,454, drawn in part to methods of treatment or prevention of inflammation.

For at least the preceding reasons, the provisional rejections of claims 11-31 under the judicially created doctrine of obviousness type double patenting over claims 16-33 of co-pending Application Ser. No. 10/547,455 and claims 13-24 of co-pending Application Ser. No. 10/547,454 are overcome. Applicant respectfully requests that the Examiner withdraw these rejections.

Obviousness Rejections under 35 U.S.C. § 103(a)

Claims 11-31 stand rejected under 35 U.S.C. § 103(a) as being obvious over Fukunaga, U.S. Pat. No. 5,677,290 (Fukunaga '290) in view of Fukunaga, et al. U.S. Pat. No. 5,679,650 (Fukunaga et al. '650) and further in view of Ueeda et al., Life Sciences, 49(18), 1351-1358 (1991) (Ueeda et al.).

However, the present claims are not obvious in view of these references, because neither Fukunaga '290 nor Fukunaga et al. '650 teach or suggest alkoxy substituted adenosines, let alone the spongosine (2-methoxyadenosine) of the claimed method, while the Ueeda et al. reference teaches that substituted adenosines which are in the Fukunaga patents have substantially different binding and selectivity properties compared to 2-ethoxyadenosine. Consequently, one of ordinary skill in the art would not combine these references to arrive at the claimed method of preventing, treating, or ameliorating pain which comprises administering spongosine (2-methoxyadenosine) to a subject in need of such prevention, treatment, or amelioration.

For example, according to Fukunaga '290, "[t]he term "adenosine compound" denotes compounds such as adenosine and adenine nucleotides, as well as derivatives and analogs of adenosine and ATP. As used in Fukunaga '290, the "adenine nucleotides" are adenosine monophosphate, adenosine diphosphate, and adenosine triphosphate. In general, the preferred adenine nucleotide is adenosine triphosphate (ATP)" (Fukunaga '290, col. 3, ll 53-59). Consequently, not only does Fukunaga '290 not disclose "2-methoxyadenosines in any method of treatment," as acknowledged by the Examiner, Fukunaga '290 does not teach or suggest alkoxy substituted adenosines or 2-substituted adenosines, let alone the claimed method which comprises administering spongosine (2-methoxyadenosine).

Further, Fukunaga et al. '650 teaches that a purine compound has undesired effects unless combined with a counteracting agent, e.g., catecholamine, and because "purine compounds such as adenosine are considered toxic at concentrations that have to be administered to a patient to maintain efficacious extracellular therapeutic level, the administration of adenosine alone has been considered of no use or limited therapeutic use" (Fukunaga et al. '650, abstract and col. 2, ll 38-43). Consequently, Fukunaga et al. '650 teaches away from the present invention, which does not require a counteracting agent. Furthermore, Fukunaga et al. '650 teaches that a purine compound is selected from adenosine, phosphorylated adenosine, 5'-N-ethylcarboxamidoadenosine (NECA), R(-)N^6-(2-phenylisopropyl) adenosine (*R*-PIA), 2-chloroadenosine, N^6 -cyclopentyladenosine, and N^6-cyclohexyladenosine (claim 1 and col. 11, ll 26-32). Consequently, Fukunaga et al. '650 does not disclose "2-methoxyadenosine as an active ingredient in any method of treatment," as acknowledged by the Examiner. Moreover, Fukunaga et al. '650 does not teach or suggest alkoxy substituted adenosines or 2-alkoxy substituted adenosines, let alone the claimed method which comprises administering spongosine (2-methoxyadenosine).

The Ueeda, et al. reference does not remedy the defects of the Fukunaga references. The Ueeda, et al. reference, directed to structure–activity relationships of adenosines at the A_1AR and A_2AR adenosine receptors of rat and guinea pig, is silent regarding analgesia of adenosines and does not disclose spongosine (2-methoxyadenosine). The Examiner alleges that the Ueeda, et al.

reference discloses at page 1353 that "2-ethoxyadenosine has binding constants at adenosine receptors that vary very little from the binding constants for adenosine, for R-PIA and for NECA, a teaching supporting the conclusion that substitution of an adenosine analog for adenosine would be expected to produce a similar effect, including the analgesic effect." Contrary to the Examiner's allegation, Table I at page 1353 of the Ueeda, et al. reference discloses no binding constant whatsoever for adenosine at A_1AR or A_2AR adenosine receptors, "because adenosine deaminase is added to the assay medium to destroy endogenous adenosine" (Ueeda, et al., p. 1353, Table I & fn a). Furthermore, differences between the "**–log** inhibition constant, K_i (M)" (emphasis added) values in Table I correspond to substantial differences in the inhibition constant K_i[1] between 2-ethoxyadenosine (#13) and compounds found in Fukunaga et al. '650, such as 5'-N-ethylcarboxamidoadenosine (NECA, #2), 2-chloroadenosine (#3), N^6 – cyclopentyladenosine (#4) and R(-)N^6-(2-phenylisopropyl) adenosine (*R*-PIA) (#5). For example, the inhibition constant K_i for A_1A receptor in rat and guinea pig for compounds #2-5 differ from K_i for 2-ethoxyadenosine (#13) by a factor of between 132 and 2880[2]. In particular, the inhibition constant K_i for 2-chloroadenosine at A_1AR differs from that for 2-ethoxyadenosine (#13) by a factor of 132 in rat and 170 in guinea pig. Furthermore, according to the Ueeda, et al. reference, 2-ethoxyadenosine (#13) is selective for the A_2AR receptor, whereas compounds #1-3 are unselective and compounds 4 and 5 are selective for the A_1AR receptor (Ueeda, et al., page 1354, lines 3-4). Consequently, because the Ueeda, et al. reference teaches that there are substantial differences between 2-ethoxyadenosine and adenosines disclosed in Fukunaga et al. '650, even 2-chloroadenosine, one of ordinary skill in the art would not select 2-alkoxyadenosines such as spongosine (2-methoxyadenosine), but would be led to compounds similar to those disclosed in Fukunaga '290 or Fukunaga et al. '650.

Therefore, because neither Fukunaga '290 nor Fukunaga et al. '650 teach or suggest alkoxy substituted adenosines, let alone the spongosine (2-methoxyadenosine) of the claimed method, while the Ueeda et al. reference teaches that substituted adenosines which are in the

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[1] Calculated as $K_i = 10^{(\log \text{ inhibition constant, Ki (M)})}$

[2] The ratio of the respective K_is calculated from the "–log inhibition constant, Ki (M)" in Table 1.

Fukunaga patents have substantially different binding and selectivity properties compared to 2-ethoxyadenosine, one of ordinary skill in the art would not combine these references to arrive at the claimed method of preventing, treating, or ameliorating pain which comprises administering spongosine (2-methoxyadenosine) to a subject in need of such prevention, treatment, or amelioration. Because the present claims are thus nonobvious in view of these references, Applicant respectfully requests that the Examiner withdraw the corresponding rejection.

Information Disclosure Statement

Applicant respectfully requests that the Examiner return a copy of the accompanying information disclosure statement submitted August 3, 2007, wherein all disclosure entries have been initialed by the Examiner to document his full consideration of each disclosed reference.

CONCLUSION

For the reasons set forth above, Applicants submit that the claims of the instant application, as amended herein, are in condition for allowance. Reconsideration and withdrawal of the Examiner's objections and rejections are hereby requested. Allowance of the claims is earnestly solicited.

In the event that a telephone conversation could expedite the prosecution of this application, the Examiner is requested to call the undersigned at (650) 839-5078.

The excess claim fees in the amount of $750 is being paid concurrently herewith on the Electronic Filing System (EFS) by way of Deposit Account authorization. Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date: November 19, 2007

Kraig K. Anderson
Reg. No. 54,961

Customer No. 26161
Fish & Richardson P.C.
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COPY Attorney's Docket No.: 13425-170US1 / BV-1083 US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Peter Richardson	Art Unit	: 1623
Serial No.	: 10/537,564	Examiner	: Lawrence E. Crane, Ph.D.
Filed	: August 28, 2006	Conf. No.	: 4551
Title	: USE OF SPONGOSINE FOR THE TREATMENT OF PAIN		

MAIL STOP AMENDMENT
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

INFORMATION DISCLOSURE STATEMENT

Applicants request consideration of the references listed on the attached PTO-1449 form. Under 37 C.F.R. § 1.98 (a)(2)(ii), only copies of foreign patent documents and/or non-patent literature are enclosed. Copies of any listed U.S. patents or U.S. patent application publications can be provided upon request. A copy of a communication from a foreign patent office in a PCT application PCT/GB2003/005379 is also enclosed.

The Examiner's attention is brought to Applicant's U.S. Applications Serial No. 10/547,454, filed June 28, 2006, Serial No. 10/547,455, filed July 26, 2006, Serial No. 10/547,462, filed October 26, 2006, and Serial No. 10/598,520, filed September 1, 2006.

The late submission fee under §1.17(p) in the amount of $180 is being paid concurrently herewith on the Electronic Filing System (EFS) by way of Deposit Account authorization. Please apply any other charges or credits to Deposit Account No. 06 1050.

Respectfully submitted,

Date: Aug 9, 2007

Kraig K. Anderson
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21695401.doc

Substitute Form PTO-1449 (Modified)	U.S. Department of Commerce Patent and Trademark Office	Attorney's Docket No. 13425-170US1	Application No. 10/537,564
Information Disclosure Statement by Applicant (Use several sheets if necessary)		Applicant Peter Richardson	
(37 CFR §1.98(b))		Filing Date August 28, 2006	Group Art Unit 1623

U.S. Patent Documents

Examiner Initial	Desig. ID	Document Number	Publication Date	Patentee	Class	Subclass	Filing Date If Appropriate
	AA	3,936,439	02/03/1976	Marumoto, *et al.*			
	AB	4,225,591	09/30/1980	Marumoto, *et al.*			
	AC	4,255,565	03/10/1981	Marumoto, *et al.*			
	AD	4,705,758	11/10/1987	Bruns			
	AE	5,877,180	03/02/1999	Linden, *et al.*			

Foreign Patent Documents or Published Foreign Patent Applications

Examiner Initial	Desig. ID	Document Number	Publication Date	Country or Patent Office	Class	Subclass	Translation Yes	Translation No
	AF	AU 49412/72	05/30/1974	Australia				
	AG	DE 2258378	06/14/1973	Germany			Corresponding to AU 4941272	
	AH	FR 2162128	07/13/1973	France			Corresponding to AU 4941272	
	AI	WO 199638728	12/05/1996	WIPO				
	AJ	WO 199934804	07/15/1999	WIPO				
	AK	WO 2004079329	09/16/2004	WIPO				

Other Documents (include Author, Title, Date, and Place of Publication)

Examiner Initial	Desig. ID	Document
	AL	"Aldrich Handbook of Fine Chemicals and Laboratory Equipment," 1015-1016, (2000); XP002366927.
	AM	Askalan, R. et al., "Role of Histidine Residues in the Adenosine A2A Receptor Ligand Binding Site," *Journal of Neurochemistry*, 63(4):1477-84, (1994); XP001196996.
	AN	Bartlett, R. et al., "Synthesis and Pharmacological Evaluation of a Series of Analogues of 1-Methylisoguanosine," *Journal of Medicinal Chemistry*, 24:947-54, (1981); XP002225573.
	AO	Belardinelli, L. & Isenberg, G., "Isolated Atrial Myocytes: Adenosine and Acetylcholine Increase Potassium Conductance," *The American Journal of Physiology*, 224:H734-H737, (1983).
	AP	Belfrage, M. et al., "The Safety and Efficacy of Intrathecal Adenosine in Patients with Chronic Neuropathic Pain," *Anesthesia and Analgesia*, 89(1):136-42, (1999); XP009027670.
	AQ	Bhakuni, D., "Biological Activity of Marine Nucleosides and their Analogues," *Proceedings of the Indian National Science Academy*. Part B Biological Sciences, 65(Part 2):97-112, (1995); XP001165752.
	AR	Bressi, J. et. al., "Adenosine Analogues as Inhibitors of Trypanosoma Brucei Phosphoglycerate Kinase: Elucidation of a Novel Binding Mode for a 2-Amino-N6-Substituted Adenosine," *Journal of Medicinal Chemistry*, 43(22):4135-50, (2000); XP000999137.

Examiner Signature	Date Considered

EXAMINER: Initials citation considered. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Substitute Form PTO-1449 (Modified) U.S. Department of Commerce Patent and Trademark Office	Attorney's Docket No. 13425-170US1	Application No. 10/537,564
Information Disclosure Statement by Applicant (Use several sheets if necessary) (37 CFR §1.98(b))	Applicant Peter Richardson	
	Filing Date August 28, 2006	Group Art Unit 1623

Other Documents (include Author, Title, Date, and Place of Publication)		
Examiner Initial	Desig. ID	Document
	AS	Collins, S. et al., "The Effect of GR190178, a Selective Low-Efficacy Adenosine A1 Receptor Agonist, on the Treatment of Neuropathic Hyperalgesia in the Rat," *British Journal of Pharmacology*, 133(Proceedings Supplement):48p (2001), Proceedings of the British Pharmacological Society Meeting, (Dec. 18-21, 2000); XP009027671.
	AT	Daly, J. et al., "Structure-Activity Relationships for N6-Substituted Adenosines at a Brain A1-Adenosine Receptor with a Comparison to an A2-Adenosine Receptor Regulating Coronary Blood Flow," *Biochemical Pharmacology*, 35(15):2467-81 (1986) XP009010090
	AU	Dan, K., "Nerve Block Therapy and Postherpetic Neuralgia," *Critical Reviews in Physical and Rehabilitation Medicine*, 7(2):93-112 (1995) Embase Database Accession No. EMB-1995373280. XP002273335
	AV	De Zwart, M. et al., "5'-N-Substituted Carboxamidoadenosines as Agonists for Adenosine Receptors," *Journal of Medicinal Chemistry*, 42(8): 1384-92 (1999) XP001002032
	AW	Deghati, P. et al., ""Regioselective Nitration of Purine Nucleosides: Synthesis of 2-Nitroadenosine and 2-Nitroinosine," *Tetrahedron Letters*, 41(8):1291-5 (2000) XP004188609
	AX	Feoktistov, I. et al., "Adenosine A2B Receptors: A Novel Therapeutic Target in Asthma?," *Trends in Pharmacological Sciences*, 19(4):148-53 (1998) XP002287445
	AY	Fishman, P. et al., "A3 Adenosine Receptor as a Target for Cancer Therapy," *Anti-Cancer Drugs*, 13(5):437-43 (2002) XP009024520
	AZ	Hiley, C. et al., "Effects of pH on Responses to Adenosine, CGS 21680, Carbachol and Nitroprusside in the Isolated Perfused Superior Mesenteric Arterial Bed of the Rat," *British Journal of Pharmacology*, 116(6):2641-2646 (1995) XP008032448
	AAA	Jiang, Q. et al., "Mutagenesis Reveals Structure-Activity Parallels Between Human A2A Adenosine Recveptors and Biogenic Amine G Protein-Coupled Receptors," *Journal of Medicinal Chemistry*, 40(16):2588-95 (1997) XP002287314
	ABB	Kaul, P. et al., "Adenosine Agonist of Marine Origin Indicative of Two Types of Adenosinergic Receptors," *Pharmacologist*, 23(3):540 (1981) XP009027638
	ACC	Keeling, S. et al., "The Discovery and Synthesis of Highly Potent, A2a Receptor Agonists," *Bioorganic and Medicinal Chemistry Letters*, 10(4):403-6 (2000) XP004189943
	ADD	Kirk, I. et al., "Further Characterization of [3H]-CGS 21680 Binding Sites in the Rat Striatum and Cortex," *British Journal of Pharmacology*, 114(2):537-43 (1995) XP008032472
	AEE	Klitgaard, H. et al., "Contrasting Effects of Adenosine A_1 and A_2 Receptor Ligands in Different Chemoconclusive Rodent Models," *European Journal of Pharmacology*, 242:221-8 (1993)
	AFF	Knabb, R. et al., "Consistent Parallel Relationships Among Myocardial Oxygen Consumption, Coronary Blood Flow, and Pericardial Infusate Adenosine Concentration with Various Interventions and Beta-Blockade in the Dog," *Circulation Research*, 53:33-41 (1983)
	AGG	König, G., "Meeresorganismen als Quelle Pharmazeutisch Bedeutsamer Naturstoffe," *Deutsche Apotheker Zeitung*, 132(14):673-83 (1992) XP002255617
	AHH	Marumoto, R. et al. "Synthesis and Coronary Vasodilating Activity of 2-Substituted Adenosines," *Chemical and Pharmaceutical Bulletin*, 23(4):759-74 (1975) XP002154408
	AII	Matova, M. et al. "QSAR Analysis of 2-Alkyloxy and 2-Aralkyloxy Adenosine A1- and A2-Agonists," *European Journal of Medicinal Chemistry*, 32(6):505-13 (1997) XP004088461
	AJJ	Matsuda et al., Nucleosides and Nucleotides. XXVII. Synthesis of 2- and 8-Cyanoadenosines and their Derivatives," *Chemical and Pharmaceutical Bulletin*, 27(1):183-92 (1979) XP002127436

Examiner Signature	Date Considered

EXAMINER: Initials citation considered. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Substitute Form PTO-1449 (Modified)	U.S. Department of Commerce Patent and Trademark Office	Attorney's Docket No. 13425-170US1	Application No. 10/537,564
Information Disclosure Statement by Applicant (Use several sheets if necessary)		Applicant Peter Richardson	
(37 CFR §1.98(b))		Filing Date August 28, 2006	Group Art Unit 1623

Other Documents (include Author, Title, Date, and Place of Publication)		
Examiner Initial	Desig. ID	Document
	AKK	Matsuda, A. et al., "Nucleosides and Nucleotides. 103. 2-Alkyladenosines: a Novel Class of Selective Adenosine A2 Receptor Agonists with Potent Antihypertensive Effects," *Journal of Medicinal Chemistry*, 35:241-52 (1992) XP002170995
	ALL	Miles, R. et al., "Nucleic Acid Related Compounds," *Journal of the American Chemical Society*, 117:5951-7 (1995) XP002366161
	AMM	Nair, V. et al., "Novel, Stable Cogeners of the Antiretroviral Compound 2', 3'-Dideoxyadenosine," *Journal of the American Chemical Society*, 111(22):8502-4 (1989) XP001105896
	ANN	Ojha, L. et al., "A Simple Method for Synthesis of Spongosine, Azaspongosine, and their Antiplatelet Effects," *Nucleosides and Nucleotiodes*, 14(9-10):1889-1900 (1995) XP009027643
	AOO	Okusa, M., "A2A Adenosine Receptor: A Novel Therapeutic Target in Renal Disease," *American Journal of Physiology*, 282(1 Part 2):F10-F18 (2002) XP002287448
	APP	Rieger, J.M. et al., "Design, Synthesis, and Evaluation of Novel A2A Adenosine Receptor Agonists," *Journal of Medicinal Chemistry*, 44:531-9 (2001) XP002222174
	AQQ	Ribeiro, J. et al., "Adenosine Receptors in the Nervous System: Pathophysiological Implications," *Progress in Neurobiology*, 68(6):377-92 (2002) XP002287447
	ARR	Sawynok, J. "Adenosine Receptor Activation and Nociception," *European Journal of Pharmacology*, 317(1):1-11 (1998) XP002273334
	ASS	Schaeffer, H. et al., "Synthesis of Potential Anticancer Agents. XIV. Ribosides of 2, 6-Disubstituted Purines," *Journal of the American Chemical Society*, 80:3738-42 (1958) XP002300926
	ATT	Smith, J. et al., "The Effects of Reduced pH on A2B Adenosine Receptor-Evoked Cyclic AMP Generation in the Guinea-Pig Cerebral Cortex," *British Journal of Pharmacology*, 123 (Proc. Suppl.): 195p (1998). Meeting of the British Pharmacological Society Held Jointly with the Dutch Pharmacological Society (Dec. 10-12, 1997) XP008032489
	AUU	Sullivan, G. et al., "Role of A2A Adenosine Receptors in Inflammation," *Drug Development Research*, 45(3/4):103-12 (1998) XP000978332
	AVV	Ueeda, M. et al., "2-Alkoxyadenosines: Potent and Selective Agonists at the Coronary Artery A2 Adenosine Receptor," *Journal of Medicinal Chemistry*, 34:1334-9 (1991) XP002225574
	AWW	Ueeda, M. et al., "2-Aralkoxyadenosines: Potent and Selective Agonists at the Coronary Artery A2 Adenosine Receptor," *Journal of Medicinal Chemistry*, 34(4):1340-4 (1991) XP004088461
	AXX	Umino, T. et al., "Nucleosides and Nucleotides. 200. Reinvestigation of 5'-N-Ethylcarboxamidoadenosine Derivatives: Structure-Activity Relationships for P(3) Purinoceptor-Like Proteins," *Journal of Medicinal Chemistry*, 44:208-14 (2001) XP002366162
	AYY	Vittori, S. et al., "2-Alkenyl and 2-Alkyl Derivatives of Adenosine and Adenosine-5'-N-Ethyluronamide: Different Affinity and Selectivity of E- and Z-Diastereomers at A2A Adenosine Receptors," *Journal of Medicinal Chemistry*, 39:4211-7 (1996) XP002366163
	AZZ	Copy of International Search Report for PCT/GB2003/05379, by Examiner S. Allnutt,- dated March 22, 2006.

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Search results: 5 Item(s)

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Title Melloni's illustrated **medical dictionary** / Ida G. Dox ... [et al.]
Edition 4th ed.
Publisher New York : Parthenon, c2002
Description xiii, 764 p. : ill. (some col.) ; 29 cm.
Note Rev. ed. of: Melloni's illustrated **medical dictionary** / Ida G. Dox, B. John Melloni, Gilbert M. Eisner. 3rd ed. 1993
ISBN 185070094X (alk. paper)
Language English
Subject Medicine -- Dictionaries
Medicine -- **Dictionary** -- English
Médecine -- Dictionnaires anglais
Added Entry Dox, Ida
Melloni, Biagio John
Dox, Ida. Melloni's illustrated **medical dictionary**
Format Book
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Library	Call Number	Availability	Notes
UC Berkeley			
HealthSci	R121 .D76 2002	Circ status	Reference
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FOURTH EDITION

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BOCA RATON LONDON NEW YORK WASHINGTON, D.C.

The Fourth Edition *of Melloni's Illustrated Medical Dictionary* is published by:

The Parthenon Publishing Group
23–25 Blades Court
Deodar Road
London
SW15 2NU, UK

The first and second editions of this book were published by Williams and Wilkins, and the third by The Parthenon Publishing Group.

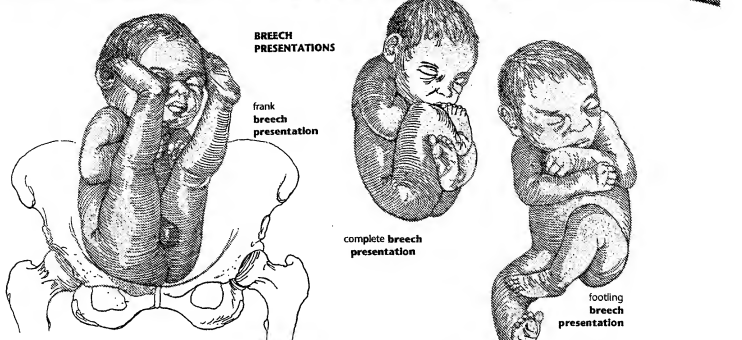
FOURTH EDITION

ISBN: 1-85070-094-X

British Library Cataloguing-in-Publication Data available on request

Library of Congress Cataloging-in-Publication Data
Melloni's illustrated medical dictionary / Ida G. Dox...[et al.]. - 4th ed.
p.; cm.
Rev. ed. of: Melloni's illustrated medical dictionary / Ida G. Dox, B. John Melloni, Gilbert M. Eisner, 3rd ed. c1993
ISBN 1-85070-094-X (alk. paper)
1. Medicine - Dictionaries. I. Title: Illustrated Medical Dictionary. II. Dox, Ida. III. Melloni, Biagio John.
[DNLM: 1. Medicine—Dictionary—English. W 13 M5271 2001]
R121.D76 2001
610'.3—dc21

2001045162



under asynclitism.

breech p. Presentation of the fetal pelvis; called *frank breech p.* when the legs of the fetus extend fully over the anterior surface of its body; *complete breech p.* when both thighs and legs are flexed; *footling breech p.* when one or both legs are extended below the level of the fetal buttocks.

cephalic p. Presentation in which the head is the presenting part; called *bregma p.*, *vertex p.* when the occipital portion of the head is the presenting part, the head is flexed and the chin and thorax in contact; *sinciput p.* when the large fontanel is the presenting part; *brow p.* when the brow is the presenting part; *face p.* when the face is the presenting part, the head is sharply extended with the occipital portion in contact with the fetal back. Also called head presentation.

head p. See cephalic presentation.

placental p. See placenta previa, under placenta.

posterior parietal p. See posterior asynclitism, under asynclitism.

shoulder p. Presentation in which the long axis of the fetus lies transversely with the maternal long axis and a shoulder is the presenting part.

preservative (pre-zer'vă-tiv) **1.** A substance added to food products, such as fatty acids, for inhibiting the growth of food-spoiling bacteria. **2.** Capable of preserving.

presomite (pre-so'mīt) In embryology, before the appearance of somites.

pressor (pres'or) Causing constriction of blood vessels and a rise in blood pressure; said of certain substances and nerve fibers.

pressoreceptor (pres-o-re-sep'tor) See baroreceptor.

pressure (presh'ur) A force exerted or acting against resistance.

atmospheric p. The pressure exerted by the atmosphere; approximately 15 pounds per square inch at sea level, capable of supporting a column of mercury 760 millimeters high.

back p. Pressure exerted in the circulatory system resulting from obstruction to flow.

blood p. The pressure of the circulating blood on the walls of the arteries, primarily maintained by the contraction of the left ventricle, the resistance of the arterioles and capillaries, the elasticity of the arterial walls, and the volume and viscosity of the blood; the maximum or systolic blood pressure occurs at the moment of systole of the left ventricle of the heart; the minimum or diastolic blood pressure occurs during diastole of the ventricle; the upper limits of normal in adults are generally set at 140/90 mmHg.

central venous p. (CVP) Pressure of blood in the superior or inferior vena cava.

cerebrospinal p. Tension of the cerebrospinal fluid, normally 100 to 150 mm of water (measured by lumbar puncture).

continuous positive airway p. (CPAP) Respiratory therapy in which pressure within the lung airways is mechanically maintained above atmospheric pressure throughout the respiratory cycle to prevent collapse of the airways.

critical p. The pressure required to condense or liquefy a gas at the critical temperature.

diastolic p. Arterial pressure during diastole; see blood pressure.

effective osmotic p. The portion of the total osmotic pressure of a solution that regulates the tendency of its solvent to pass through a boundary, such as a semipermeable membrane.

hydrostatic p. In a closed fluid system at rest, the pressure exerted at any level by the weight of the fluid above it.

hyperbaric p. Pressure higher than normal atmospheric pressure; used in therapy for shock, carbon dioxide poisoning, clostridial infections, and for some operations.

intracranial p. (ICP) Pressure within the skull.

intraocular p. (IOP) Pressure of the fluid within the eye, measured by a tonometer, usually in millimeters of mercury (mmHg). Also called intraocular tension; ocular tension.

negative p. A pressure lower than that of ambient atmosphere.

occlusal p. Any force exerted upon the occlusal surfaces of teeth.

oncotic p. Osmotic pressure exerted by colloids in solution.

osmotic p. Pressure or stress exerted by dissolved substances on a semipermeable membrane that separates a solution from the pure solvent.

partial p. The portion of the total pressure exerted by each component of a gas mixture, expressed in millimeters of mercury (mmHg).

positive end-expiratory p. (PEEP) Technique used in respiratory therapy to increase the amount of gases remaining in the lungs after expiration by maintaining pressure within the airways.

pulmonary p. Pressure in the pulmonary artery.

pulmonary capillary wedge p. Pressure obtained by wedging the tip of a catheter in a small pulmonary artery; blocking blood flow provides an indirect measure of the pressure in the left atrium of the heart.

pulse p. The difference between the systolic (maximum) and diastolic (minimum) blood pressures within an artery during the cardiac cycle; it normally varies between 30 and 50 mmHg.

systolic p. Arterial pressure during systole; see blood pressure.

vapor p. The pressure exerted by the molecules of a vapor in equilibrium with its solid or liquid phase.

presynaptic (pre-sĭ-nap'tik) **1.** Existing or taking place before a synapse is crossed. **2.** Situated proximal to a synapse.

presystole (pre-sis'to-le) The interval immediately preceding the systole.

pretibial (pre-tib'e-al) Pertaining to the front of the leg, especially that portion in front of the tibia.

prevalence (prev'ă-lens) The number of people with a specific condition in a given population.

preventive (pre-ven'tiv) Acting to ward off or hinder the occurrence of something such as a disease.

prevertebral (pre-ver'te-bral) In front of a vertebra or of the vertebral column.

prevesical (pre-ves'ĭ-kal) In front of the bladder.

Prevotella melaninogenica A species of nonmotile, gram-negative bacteria (genus *Prevotella*) found in the oral cavity; feces; and infections of the intestinal, respiratory and genitourinary tracts. Implicated in periodontal disease. Also called *Bacteroides melaninogenicus*.

priapism (prī'ă-piz-m) A continuous and pathologic erection of the penis without sexual desire; usually associated with certain diseases, especially sickle cell disease.

primacy (prī'mă-sē) The state of being primary.

primaquine phosphate (prim'ă-kwin fos'fāt) Bitter, orange crystals, soluble in water; used in the treatment of malaria.

primary (prī'mer-e) **1.** Occurring first; not secondary. **2.** First in a sequence or importance. **3.** The simplest or most primitive form.

primate (prī'māt) A member of the order Primates.

Primates (prī-ma'tēz) The highest order of mammals, including man and such animals as apes, monkeys, and lemurs.

primigravida (prī-mĭ-grav'ĭ-dă) A woman who has been pregnant only once. Also called gravida 1.

primipara (prī-mip'ă-ră) A woman who has completed one pregnancy to the stage of viability, regardless of whether it was a single or multiple birth, or whether the fetus was live or stillborn. Also called para 1.

primiparous (prī-mip'ă-rus) Denoting a primipara.

primitive (prim'ĭ-tiv) Primary; embryonic.

primordial (prī-mor'de-al) **1.** Relating to the embryonic group of cells that develops into an organ or structure. **2.** Formed during the early stage of development.

primordium (prī-mor'de-um) The earliest cells forming an organ or structure in the embryo; usually denoting a theoretical stage later than anlage.

principle (prin'sĭ-pl) **1.** A fundamental concept. **2.**

Search results: 86 Item(s)

Item 13 of 86 Total

Return to Search Results List

Title Mosby's **medical**, nursing, and allied health **dictionary** / revision editor, Kenneth N. Anderson ; consulting editor and writer, Lois E. Anderson ; consulting and pronunciation editor, Walter D. Glanze.

Edition 4th ed.

Publisher St. Louis, MO : Mosby, c1994.

Description xxxiii, 43, 1973 p. : col. ill. ; 26 cm.

Note Includes bibliographical references.

ISBN 0801672252 (Professional) 0815161131 0815161115 (Trade)

Language English

Subject Nursing -- Dictionary.
Dictionaries, Medical.
Nursing -- Dictionaries.
Medicine -- Dictionaries.

Added Entry Anderson, Kenneth, 1921-
Anderson, Lois E.
Glanze, Walter D.

Format Book

Library UC Los Angeles UC San Diego UC Irvine UC San Francisco UC Berkeley UC Davis All

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Cover illustrations:
Retina from *Selected Topics in Ophthalmology*, Medcom Clinical Lecture Guides, Garden Grove, California, 1973, Medcom, Inc.
Blood cells from Hayhoe FGJ and Flemans RJ *Color Atlas of Hematological Cytology*, ed. 3. London, 1992, Wolfe Publishing, Ltd.
Chest tube drainage system and **triceps skinfold calipers** from Potter PA and Perry AG, *Fundamentals of Nursing: Concepts, Process, and Practice*, ed. 3. St. Louis, 1993, Mosby–Year Book, Inc.
Positron emission tomography from Perkin GD, Rose FC, Blackwood W, and Shawdon HH. *Atlas of Clinical Neurology*. London, 1986, Gower Medical Publishing.

FOURTH EDITION

Printed in the United States of America
Composition by The Clarinda Company
Printing/binding by Rand McNally

Mosby–Year Book, Inc.
11830 Westline Industrial Drive
St. Louis, Missouri 63146

Library of Congress Cataloging in Publication Data
Mosby's medical, nursing, and allied health dictionary / revision editor, Kenneth N. Anderson; consulting editor and writer, Lois E. Anderson; consulting and pronunciation editor, Walter D. Glanze.—4th ed.
p. cm.
Includes bibliographical references.
ISBN 0-8016-7225-2 (Professional).—ISBN 0-8151-6113-1.—ISBN 0-8151-6111-5 (Trade)
1. Medicine—Dictionaries. 2. Nursing—Dictionaries. I. Anderson, Kenneth, 1921– . II. Anderson, Lois E. III. Glanze, Walter D. IV. Title: Medical, nursing, and allied health dictionary.
[DNLM: 1. Nursing—dictionaries. W 13 M8941 1993]
R121.M89 1993
610'.3—dc20
DNLM/DLC
for Library of Congress 93-39959
CIP

93 94 95 96 97 / 9 8 7 6 5 4 3 2 1

veins of the area. 2. edema of the fetal scalp after cephalic presentation.

pressure necrosis. See **decubitus ulcer.**

pressure point, 1. a point over an artery where the pulse may be felt. Pressure on the point may be helpful in stopping the flow of blood from a wound distal to the point. 2. a site that is extremely sensitive to pressure, such as the phrenic pressure point along the phrenic nerve between the sternocleidomastoid and the scalenus anticus on the right side; pressure at this site may be symptomatic of gallbladder dysfunction.

pressure-sensitive adhesive, a drug-delivery device that uses polymers that are permanently tacky at room temperature and will adhere to the skin when slight pressure is applied.

pressure sore. See **decubitus ulcer.**

pressure support ventilation (PSV), the augmentation for spontaneous breathing effort with a specific amount of positive airway pressure. The patient initiates the inspiratory flow, generating his or her own V_t and frequencies.

pressure ventilator, a ventilator in which gas delivery is limited by a predetermined pressure.

pressure ulcer. See **decubitus ulcer.**

presumptive signs /-sump'tiv/ [L, *praesumere*, to take beforehand; *signum*, mark], manifestations that indicate a pregnancy although they are not necessarily positive. Presumptive signs may include cessation of menses and morning sickness. See also **Chadwick's sign.**

preswing stance stage /prē'swing/ [L, *prae* + AS, *swingan*, to fling; L, *stare*, to stand; OFr, *estage*, stage], one of the five stages in the stance phase of walking or gait, involving a brief transitional period of double limb support during which one leg of the body is rapidly relieved of bodybearing weight and prepared for the swing forward. The type of preswing used by an individual is a factor in the diagnoses of many abnormal orthopedic conditions. Compare **initial contact stance stage, loading response stance stage, midstance, terminal stance.** See also **swing phase of gait.**

presymptomatic disease /-simp'təmat'ik/ [L, *prae* + Gk, *symptoma*, a happening], an early stage of disease when physiologic changes have begun although no signs or symptoms are observed.

presynaptic /-sinap'tik/ [L, *prae* + *synaptein*, to join], 1. situated near or before a synapse. 2. before a synapse is crossed.

presystole /-sis'təlē/ [L, *pre*, before; Gk, *systole*, contraction], an interval in the cardiac cycle immediately before systole.

presystolic /-sistol'ik/ [L, *prae* + Gk, *systole*, contraction], of or pertaining to the period preceding systole.

presystolic murmur [L, *pre*, before; Gk, *systole*; L, *murmur*, humming], a heart mumur in cases of mitral stenosis, before diastole.

preterm /prēturm'/ [L, *pre*, before; Gk, *terma*, limit], 1. events before a specific date. 2. pertaining to a shorter than normal period of gestation.

preterm birth, any birth that occurs before the thirty-seventh week of gestation. See also **premature infant.**

rash on the anterior surface of the legs. Also called **Fort Bragg fever.**

pretrial discovery. See **discovery.**

prevalence /prev'ələns/ [L, *praevalentia*, a powerful force], (in epidemiology) the number of all new and old cases of a disease or occurrences of an event during a particular period of time. Prevalence is expressed as a ratio in which the number of events is the numerator and the population at risk is the denominator. See also **rate.**

prevention /-ven'shən/ [L, *praevenire*, to anticipate], (in nursing care) any action directed toward preventing illness and promoting health to avoid the need for secondary or tertiary health care. Prevention includes such nursing actions as assessment; application of prescribed measures, such as immunization; health teaching; early diagnosis and treatment; and recognition of disability limitations and rehabilitation potential. In acute care nursing, many interventions are simultaneously therapeutic and preventive.

preventive /-ven'tiv/ [L, *praevenire*, to anticipate], tending to slow, stop, or interrupt the course of an illness or to decrease the incidence of a disease.

preventive care, a pattern of nursing and medical care that focuses on the prevention of disease and health maintenance and includes early diagnosis of disease, discovery and identification of people at risk of developing specific problems, counseling, and other intervention to avert a health problem. Screening tests, health education, and immunization programs are common examples of preventive care. Also called **primary nursing.**

preventive dentistry [L, *praevenire*, to anticipate + *dens*, tooth], the science of the prevention of disease affecting the teeth.

preventive health care. See **preventive care.**

preventive medicine [L, *praevenire*, to anticipate + *medicina*], the branch of medicine that is concerned with the prevention of disease and methods for increasing the power of the patient and community to resist disease and prolong life.

preventive nursing [L, *praevenire*, to anticipate + *nutrix*, nurse], the branch of nursing that is concerned with general health promotion, teaching of early recognition and treatment of disease, encouraging lifestyle modification, and prevention of further deterioration of the disabled.

preventive psychiatry, the use of theoretical knowledge and skills to plan and implement programs designed to achieve primary, secondary, and tertiary prevention.

preventive treatment, a procedure, measure, substance, or program designed to prevent a disease from occurring or a mild disorder from becoming more severe. Various diseases are prevented by immunizations with vaccines, antiseptic measures, the avoidance of smoking, regular exercise, a prudent diet, adequate rest, the correction of congenital anomalies, and screening programs for the detection of preclinical signs of disorders. Also called **prophylactic treatment.**

previa. See **placenta previa.**

previllous embryo /prēvil'əs/ [L, *prae* + *villus*, hairy; Gk. *en* in, *bryein*, to grow], an embryo of a placental mam-

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Author Taber, Clarence Wilbur, 1870-

Uniform Title [Cyclopedic **medical dictionary**]

Title Taber's cyclopedic **medical dictionary**.

Edition Ed. 16 illustrated / edited by Clayton L. Thomas ; new illustrations by Beth Anne Willert.

Publisher Philadelphia : F.A. Davis, c1989.

Description xxxvii, 2401 p. : ill. (some col.) ; 21 cm.

Note "The nursing & allied health **dictionary**"--Cover and spine label.

Note **Dictionary** intended for nurses and other allied health personnel. Includes new terms reflecting changes and new topics in contemporary health care, e.g., AIDS, decision analysis, prescribing nurses, and clearinghouses serving consumer health needs. Biographical entries are also included. Entries give words, pronunciation, etymology, definition, subentries, abbreviation, synonyms, cross references, and colored illustrations. Miscellaneous appendixes. 1st ed., 1940; 15th ed., **1985.**

ISBN 0803683111 0803683103 (thumb indexed)

Language English

Subject Dictionaries, **Medical.**

Added Entry Thomas, Clayton L., 1921-

Format Book

Library UC Los Angeles UC Davis UC Santa Cruz All

Library	Call Number	Availability	Notes
UC Davis			
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EXHIBIT C

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EDITION 16 ILLUSTRATED

Taber's® CYCLOPEDIC MEDICAL DICTIONARY

F. A. DAVIS COMPANY PHILADELPHIA

PRINTED IN THE UNITED STATES OF AMERICA

Last digit indicates print number 10 9 8 7 6 5 4 3 2 1

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Library of Congress Cataloging in Publication Data

Taber, Clarence Wilbur, 1870–1968
Taber's Cyclopedic Medical Dictionary, edition 16.

1. Medicine—Dictionaries. I. Thomas, Clayton L., 1921– . II. Title. III. Title: Cyclopedic medical dictionary. [DNLM: 1. Dictionaries, Medical. W 13 T113d]
R121.T144 1989 610'.3'21 62-8364
ISBN 0-8036-8311-1
ISBN 0-8036-8310-3 (indexed)

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mmHg.

p., intrathoracic. Pressure within the thorax.

p., intraventricular. Pressure within the ventricles of the heart during different phases of diastole and systole.

p., negative. Any pressure less than that of the atmosphere, or less than that pressure to which the initial pressure is being compared.

p., occlusal. P., biting, q.v.

p., oncotic. Osmotic pressure exerted by colloids in a solution.

p., osmotic. The force with which a solvent, usually water, passes through a semipermeable membrane separating solutions of different concentrations. It is measured by determining the hydrostatic (mechanical) pressure that must be opposed to the osmotic force to bring the passage to a standstill.

p., partial. In a gas containing several different components, the pressure exerted by each component.

p., positive. Pressure greater than atmospheric or greater than the pressure to which the initial pressure is being compared.

p., positive end-expiratory. ABBR: PEEP. The application of slight positive pressure at the end of expiration while intermittent positive pressure is being used. This increases the amount of air remaining in the lungs at the end of expiration.

p., pre-load filling. Amount of pressure or volume in the ventricle at end diastole, measured by central venous pressure (right ventricular end-diastolic pressure) or pulmonary capillary wedge pressure (left ventricular end-diastolic pressure).

p., pulse. The difference between systolic and diastolic pressures.

p., solution. Pressure that tends to dissolve a solid present in a solution.

p., static. SEE: *static pressure.*

p., systolic. Arterial pressure at time of the contraction of the ventricles, or the ventricular systole.

p., venous. Pressure of the blood within the veins. It is highest near the periphery, diminishing progressively from capilleries to the heart. Near the heart the pressure may be below zero (negative pressure) due to negative intrathoracic pressure.

p., wedge. Pressure determined by use of a fluid-filled catheter wedged in the distal end of a branch of the pulmonary artery. This provides an indirect measurement of the pressure in the left atrium of the heart.

pressure of speech. Loud and emphatic speech that is increased in amount, accelerated, and usually difficult or impossible to interrupt. The speech is not in response to a stimulus and may continue even though no one is listening. May be present in manic episodes, organic brain disease, depression with agitation, psychotic disorders, and sometimes as an acute reaction to stress.

pressure palsy. Temporary paralysis due to pressure on a nerve trunk.

pressure paralysis. Paralysis due to pressure on the spinal cord or a nerve.

ETIOL: Injury, tumor, gummata.

pressure points. Areas for exerting pressure to control bleeding. For control of hemorrhage, pressure over bleeding point when an artery passes over a bone may be sufficient. Principal pressure points follow.

Common carotid artery, 2 in. (6 cm) above clavicle, press backwards against spine. Temporal artery, at side of face in front of ear. Occipital artery, behind mastoid process. Subclavian artery, behind clavicle, pressing down onto first rib. Axillary artery, by compression in axilla. Brachial artery, compressed by pressure at inner edge of biceps muscle halfway down arm and also above bend of elbow before artery divides into radial and ulnar arteries. Radial artery, press on thumb side of wrist against radius. Ulnar artery, press on little finger side of wrist against ulna. Deep palmar arch, in thumb opposite root of extended thumb. Abdominal artery, may be compressed against lumbar vertebrae to left of middle line when patient lies on back. Femoral artery, by abdominal wall at junction of thigh, bringing head of femur forward into groin and compressing artery against it. Popliteal artery, in popliteal space over artery. Anterior tibial artery, at front of bend of ankle. Posterior tibial artery, behind internal malleolus as it passes into foot. SEE: *bleeding* for table (Arrest of Arterial Bleeding).

pressure sore. A sore caused by pressure from a splint or other appliance, or from the body itself when it has remained immobile in bed for extended periods of time. SYN: *bedsore; decubitus ulcer.* SEE: *decubitus ulcer.* SEE: *Nursing Diagnoses* in *Appendix.*

presternum (prē-stĕr'nŭm) [L. *prae,* before, in front of, + Gr. *sternon,* chest]. The upper part of the sternum. SYN: *manubrium sterni* [NA].

presuppurative (prē-sŭp'ū-rā"tiv) [" + *sub,* under, + *puris,* pus]. Rel. to period of inflammation before suppuration.

presylvian fissure (prē-sil'vē-ăn). The anterior division of the sylvian fissure.

presymptomatic (prē"simp-tō-măt'ik). The state of health prior to the clinical appearance of the signs and symptoms of a disease.

presynaptic (prē"si-năp'tik) [" + Gr. *synapsis,* point of contact]. Located before the nerve synapse.

presystole (prē-sis'tō-lē) [L. *prae,* before, in front of, + Gr. *systole,* contraction]. The period in the heart's cycle just before the systole. SYN: *perisystole.*

presystolic (prē-sis-tŏl'ik). Before the systole of the heart.

pretarsal (prē-tär'săl) [" + Gr. *tarsos,* a broad flat surface]. In front of the tarsus.

preterm. In obstetrics, events occurring prior to the 37th week of gestation.

pretibial (prē-tib'ē-ăl) [" + *tibia,* shinbone]. In front of the tibia.

pretibial fever. A form of leptospirosis ceused by one of the several serotypes of the autumnalis serogroup. It is characterized by fever, rash on legs, prostration, splenomegaly, and respiratory disturbances. SYN: *Fort Bragg fever.*

pretympanic (prē"tim-păn'ik) [" + *tympanon,* drum]. Located in front of the tympanic membrane.

preurethritis (prē"ū-rē-thrī'tis) [" + Gr. *ourethra,* urethra, + *itis,* inflammation]. Inflammation around the urethral orifice of the vaginal vestibule.

prevalence (prĕv'ă-lĕns) [L. *praevalerie,* prevail]. The number of cases of a disease present in a specified population at a given time. SEE: *incidence.*

preventive (prē-vĕn'tiv) [ME. *preventen,* to anticipate]. Hindering the occurrence of something, esp., disease. SYN: *prophylactic.*

preventive dentistry. That phase of dentistry concerned with the maintenance of the normal masticatory apparatus by teaching good oral hygiene and dietary practice, and preserving dental health by early restorative proceduree.

preventive medicine. The branch of medicine concerned with preventing the occurrence of both mental and physical illness and disease.

There are three levele of preventive effort. Primary preventive medicine is concerned with preventing the development of disease in a susceptible or potentially susceptible population. These efforts include general promotion of health and specific protection such as immunization. Secondary preventive medicine involves early diagnosis and prompt therapy to shorten duration of illness, reduce the severity of disease, reduce possibility of contagion, and limit sequelae. Tertiary preventive medicine is important in limiting the degree of disability and promoting rehabilitation in chronic and irreversible diseases.

preventive nursing. The nurse is an essential part of the health care teem and has the opportunity to emphasize and indeed implement health care services to promote health and prevent disease. Nursing expertise and general professional competence can also be utilized in supporting community action at all levels for promoting public health measures. There are three levels of preventive nursing:

A. Primary. The goal of primary prevention is general health promotion. This includes whatever intervention ie required to provide a health-promoting environment at home, in the schools, and in the workplace by ensuring good nutrition, adequate clothing and shelter, rest and recreation, and health education (including sex education and, for the aging, realistic plans for retirement). Areas of emphasis are specific protective measures such as immunizations, environmental sanitation, accident prevention, and protection from occupational hazards. Behavior modification, though difficult, must be attempted with respect to those areas known to represent major health risk factors, i.e., smoking, obesity, improper diet, alcohol and drug abuse, and major efforts to prevent automobile accidents.

B. Secondary. Nursing care aimed at early recognition and treatment of disease. It includes general nursing interventions and teaching of early signs of disease conditions. Disease such as infectious diseases, glaucoma, and cancer *in situ* fall in this category.

C. Tertiary. Nursing care for incurable diseases, and patient instruction concerning how to manage those conditions and diseases. Parkinson's disease, multiple sclerosis, and diabetes are conditions that lend themselves to tertiary prevention. The goel is to prevent further deterioration of physical and mental function, and to have the patient utilize whatever residual function is available for maximum enjoyment of and participation in life's activities. Rehabilitation is of course an essential part of tertiary prevention.

prevertebral (prē-vĕr'tē-brăl) [L. *prae,* before, in front of, + *vertebra,* vertebra]. In front of a vertebra.

prevertebral ganglia. Ganglia of the sympathetic division of the autonomic nervous system, located near origins of the celiac and mesenteric arteries. These include the celiac and mesenteric ganglia. SYN: *collateral ganglia.*

prevertiginous (prē-vĕr-tij'i-nūe) [" + *vertigo,* a turning round]. Having a tendency to fall forward.

prevesical (prē-vĕs'i-kl) [" + *vesica,* bladder]. Located in front of the bladder.

previa, praevia (prē'vē-ă) [L.]. Appearing before or in front of.

What is Pain Medicine?

Definition of Pain Medicine

The specialty of Pain Medicine is concerned with the prevention, evaluation, diagnosis, treatment, and rehabilitation of painful disorders. Such disorders may have pain and associated symptoms arising from a discrete cause, such as postoperative pain or pain associated with a malignancy, or may be syndromes in which pain constitutes the primary problem, such as neuropathic pains or headaches. The diagnosis of painful syndromes relies on interpretation of historical data; review of previous laboratory, imaging, and electrodiagnostic studies; behavioral, social, occupational and avocational assessment; interview and examination by the pain specialist; and may require specialized diagnostic procedures, including central and peripheral neural blockade or monitored drug infusions. The special needs of the pediatric and geriatric populations are considered when formulating a comprehensive treatment plan for these patients..

The pain physician serves as a consultant to other physicians but is often the principal treating physician and may provide care at various levels, such as direct treatment, prescribing medication, prescribing rehabilitative services, performing pain relieving procedures, counseling of patients and families, direction of a multidisciplinary team, coordination of care with other healthcare providers and consultative services to public and private agencies pursuant to optimal healthcare delivery to the patient suffering from a painful disorder. The pain physician may work in a variety of settings and is competent to treat the entire range of painful disorders encountered in delivery of quality health care.

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AAPM: The Physician's Voice in Pain Medicine

Founded in 1983 as the American Academy of Algology, the American Academy of Pain Medicine (AAPM) has evolved as the primary organization for physicians practicing the specialty of Pain Medicine in the United States.

As the practice of Pain Medicine has grown, a defined body of knowledge and scope of practice have emerged, and today, Pain Medicine is recognized as a discrete specialty by the American Medical Association (AMA). AAPM is the only pain organization with representation in the AMA House of Delegates.

As a member of AAPM, you are part of a professional community of physicians with a sustained interest in pain disorders and their management. Members represent a variety of origins, including anesthesiology, internal medicine, neurology, neurosurgery, orthopedic surgery, physiatry, and psychiatry.

As a major force in advancing the practice of Pain Medicine in this country, AAPM works hard to provide you with the most up-to-date information available on the practice of Pain Medicine, to be an advocate for you, and to bring visibility and credibility to the specialty of Pain Medicine.

Mission Statement

The mission of the American Academy of Pain Medicine (AAPM) is to promote quality care of patients with pain as a symptom of disease (eudynia) and primary pain disease (maldynia) through research, education, and advocacy, and through the advancement of the specialty of Pain Medicine.

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The American Academy of Pain Medicine (AAPM) is the recognized authority on the evaluation and care of patients with pain as a symptom of disease (eudynia) and primary pain diseases (maldynia). AAPM is an influential participant in policy making for Pain Medicine services and is responsive to the needs of its members.

Definition of Pain Medicine

The specialty of Pain Medicine is concerned with the study of pain, prevention of pain, and the evaluation, treatment, and rehabilitation of persons in pain. Some conditions may have pain and associated symptoms arising from a discrete cause, such as postoperative pain or pain associated with a malignancy, or may be conditions in which pain constitutes the primary problem, such as neuropathic pains or

EXHIBIT E

headaches. The evaluation of painful syndromes includes interpretation of historical data; review of previous laboratory, imaging, and electrodiagnostic studies; assessment of behavioral, social, occupational and avocational issues; and interview and examination of the patient by the pain specialist. It may require specialized diagnostic procedures, including central and peripheral neural blockade or monitored drug infusions. The special needs of the pediatric and geriatric populations, and patients' cultural contexts, are considered when formulating a comprehensive treatment plan.

The pain physician serves as a consultant to other physicians but is often the principal treating physician and may provide care at various levels, such as direct treatment, prescribing medication, prescribing rehabilitation services, performing pain relieving procedures, counseling patients and families, directing a multidisciplinary team, coordinating care with other health care providers and providing consultative services to public and private agencies pursuant to optimal health care delivery to the patient suffering from pain. The pain physician may work in a variety of settings and is competent to treat the entire range of pain encountered in the delivery of quality health care.
